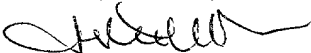


**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: YGUERABIDE et al.  
Title: ANALYTE ASSAY USING  
PARTICULATE LABELS  
Appl. No.: Unassigned  
Filing Date: Herewith  
Examiner: Unassigned  
Art Unit: Unassigned

<b>CERTIFICATE OF EXPRESS MAILING</b>	
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(Printed Name)	
	
(Signature)	

**PRELIMINARY AMENDMENT**

Commissioner for Patents  
Box Patent Application  
Washington, D.C. 20231

Sir:

Please amend the application as follows:

**In the Specification:**

Please amend the specification as follows:

Delete the first paragraph on Page 1, and insert the following paragraph:

This application is a divisional of Yguerabide et al., U.S. Application 08/953,713, filed October 17, 1997, which is a continuation-in-part of Yguerabide et al., U.S. Application 08/844,217, filed April 18, 1997, now U.S. Patent 6,214,560, which claims the benefit of Yguerabide et al., U.S. Provisional Application 60/016,383, filed April 25, 1996, all of which are incorporated herein by reference in their entireties, including drawings.

**In the Claims:**

Cancel claims 1-48 and insert the following new claims.

1           49. (New) At least one population, each said population comprising a  
2 plurality of specifically detectable metal-like light scattering particles,  
3           wherein said particles comprise at least one metal-like light scattering  
4 material, and  
5           wherein said particles have at least one additional material on their surfaces  
6 that provides chemical stability and specific binding to an analyte.

7  
8           50. (New) The population of claim 49, wherein said material does not  
9 significantly interact with light in the visible region of the spectrum.

10  
11           51. (New) The population of claim 50, wherein said at least one additional  
12 material comprises a protein, nucleic acid or peptide.

13  
14           52. (New) The population of claim 50, wherein said at least one additional  
15 material comprises a polymer.

16  
17           53. (New) The population of claim 50, wherein said at least one additional  
18 material is an organic compound or inorganic compound.

19  
20           54. (New) The population of claim 50, wherein said at least one additional  
21 material comprises a metal.

22  
23           55. (New) The population of claim 49, wherein said particles are spherical.

24  
25           56. (New) The population of claim 49, wherein said particles are oval or  
26 ellipsoidal.

27

28           57. (New) The population of claim 49, wherein said particles are  
29 asymmetrical.  
30

31           58. (New) The population of claim 49, wherein the coefficient of variation  
32 in size of said plurality of particles in a said population is less than 15%.  
33

34           59. (New) The population of claim 49, wherein the coefficient of variation  
35 in size of said plurality of particles in a said population is less than 10%.  
36

37           60. (New) The population of claim 49, wherein the coefficient of variation  
38 in size of said plurality of particles in a said population is less than 5%.  
39

40           61. (New) The population of claim 49, wherein said particles comprise a  
41 surface coat of gold.  
42

43           62. (New) The population of claim 49, wherein said particles comprise a  
44 surface coat of silver or silver alloy.  
45

46           63. (New) The population of claim 49, wherein said particles comprise a  
47 metal.  
48

49           64. (New) The population of claim 49, wherein said particles comprise gold.  
50

51           65. (New) The population of claim 49, wherein said particles comprise a  
52 mixed composition of gold and silver.  
53

54           66. (New) The population of claim 49, wherein said particles comprise gold  
55 and another metal-like material.  
56

57           67. (New) The population of claim 49, wherein said particles comprise silver  
58 and another metal-like material.

59

60           68. (New) The population of claim 49, wherein said particles comprise gold  
61 and a non-metal-like material.

62

63           69. (New) The population of claim 49, wherein said particles comprise silver  
64 and a non-metal-like material.

65

66           70. (New) The population of claim 49, wherein said particles comprise silver  
67 and a magnetic or ferro electric material.

68

69           71. (New) The population of claim 49, wherein said particles comprise gold  
70 and a magnetic or ferro electric material.

71

72           72. (New) The population of claim 49, wherein said particles are composed  
73 of a mixture of metal-like materials and a magnetic or ferro electric material.

74

75           73. (New) The population of claim 49, wherein said particles are composed  
76 of silver and gold and a magnetic or ferro electric material.

77

78           74. (New) The population of claim 49, wherein said particles have a surface  
79 coating.

80

81           75. (New) The population of claim 74, wherein said surface coating is  
82 selected from the group consisting of polymer, protein, nucleic acid, and  
83 carbohydrate.

84

85           76. (New) The population of claim 49, wherein said particles comprise gold  
86 and have an average diameter between 10 and 45 nanometers inclusive.

87

88           77. (New) The population of claim 49, wherein said particles comprise gold  
89 and have an average diameter between 50 and 70 nanometers inclusive.

90

91           78. (New) The population of claim 49, wherein said particles comprise gold  
92 and have an average diameter between 80 and 120 nanometers inclusive.

93

94           79. (New) The population of claim 49, wherein said particles comprise gold  
95 and have an average diameter greater than 120 nanometers and less than one  
96 micrometer.

97

98           80. (New) The population of claim 49, wherein said particles comprise silver  
99 and have an average diameter between 5 and 50 nanometers.

100

101           81. (New) The population of claim 49, wherein said particles comprise silver  
102 and have an average diameter between 20 and 100 nanometers.

103

104           82. (New) The population of claim 49, wherein said particles comprise silver  
105 and have an average diameter between 10 and 200 nanometers.

106

107           83. (New) The population of claim 49, wherein said particles comprise silver  
108 and have an average diameter of 120 nanometers or less.

109

110           84. (New) The population of claim 49, wherein said particles comprise silver  
111 and have a diameter selected from the group consisting of 10, 20, 30, 40, 60, and  
112 100 nm.

113

114           85. (New) The at least one population of claim 49, wherein said at least  
115 one population is two or more populations, and wherein the particles of each

population are different specifically detectable metal-like light scattering particles that specifically bind to different analytes.

86. (New) The two or more populations of claim 85, wherein said populations have size distributions with coefficients of variation less than 15%.

87. (New) The two or more populations of claim 85, wherein said populations have size distributions with coefficients of variation less than 10%.

88. (New) The two or more populations of claim 85, wherein said populations have size distributions with coefficients of variation less than 5%.

89. (New) A specifically detectable light scattering particle reagent comprising  
a population of particles formed from at least one light scattering material selected from the group consisting of a metal, a metal compound, a metal oxide, a semiconductor, and a superconductor,  
wherein said particles have an average diameter between 1 and 500 nanometers; and  
at least one base molecule bound to the surface of said particle, wherein said base molecule is adapted to bind to a binding agent,  
wherein said particle reagent specifically binds to an analyte.

90. (New) The particle reagent of claim 89, wherein said particles further have a stabilizing surface coat.

91. (New) The particle reagent of claim 90, wherein said stabilizing surface coat comprises a polymer.

146           92. (New) The particle reagent of claim 89, wherein said base molecule is  
147 bound to said binding agent.

148  
149           93. (New) The particle reagent of claim 89, wherein said particles have a  
150 plurality of different base molecules bound on the surface of said particles.

151  
152           94. (New) The particle reagent of claim 89, wherein said particles comprise  
153 a metal.

154  
155           95. (New) The particle reagent of claim 89, wherein said particles comprise  
156 gold.

157  
158           96. (New) The particle reagent of claim 89, wherein said particles comprise  
159 silver.

160  
161           97. (New) The particle reagent of claim 89, wherein said particles have an  
162 additional material on the surface that does not significantly interact with light in the  
163 visible region of the spectrum.

164  
165           98. (New) The particle reagent of claim 97, wherein said material on the  
166 surface is a protein, nucleic acid or peptide.

167  
168           99. (New) The particle reagent of claim 97, wherein said material on the  
169 surface is a metal.

170  
171           100. (New) The particle reagent of claim 89, wherein said particles are  
172 spherical.

173  
174           101. (New) The particle reagent of claim 89, wherein said particles are oval  
175 or ellipsoidal.

176

177           102. (New) The particle reagent of claim 89, wherein said particles are  
178 asymmetrical.

179

180           103. (New) The particle reagent of claim 89, wherein said population has a  
181 coefficient of variation in size of said particles of less than 15%.

182

183           104. (New) The particle reagent of claim 89, wherein said population has a  
184 coefficient of variation in size of said particles of less than 10%.

185

186           105. (New) The particle reagent of claim 89, wherein said population has a  
187 coefficient of variation in size of said particles of less than 5%.

188

189           106. (New) The particle reagent of claim 89, wherein said particles  
190 comprise a mixed composition of gold and silver.

191

192           107. (New) The particle reagent of claim 89, wherein said particles  
193 comprise gold and another metal-like material.

194

195           108. (New) The particle reagent of claim 89, wherein said particles  
196 comprise silver and another metal-like material.

197

198           109. (New) The particle reagent of claim 89, wherein said particles  
199 comprise gold and a non-metal-like material.

200

201           110. (New) The particle reagent of claim 89, wherein said particles  
202 comprise silver and a non-metal-like material.

203

204           111. (New) The particle reagent of claim 89, wherein said particles  
205 comprise silver and a magnetic or ferro electric material.



206  
207           112. (New) The particle reagent of claim 89, wherein said particles  
208 comprise gold and a magnetic or ferro electric material.

209  
210           113. (New) The particle reagent of claim 89, wherein said particles  
211 comprise a mixture of metal-like materials and a magnetic or ferro electric material.

212  
213           114. (New) The particle reagent of claim 89, wherein said particles  
214 comprise silver and gold and a magnetic or ferro electric material.

215  
216           115. (New) The particle reagent of claim 89, wherein said particles  
217 comprise silver and have a diameter selected from the group consisting of 10, 20,  
218 40, 60, and 100 nm.

219  
220           116. (New) The particle reagent of claim 89, wherein said particles  
221 comprise gold and have an average diameter between 10 and 45 nanometers  
222 inclusive.

223  
224           117. (New) The particle reagent of claim 89, wherein said particles  
225 comprise gold and have an average diameter between 50 and 70 nanometers  
226 inclusive.

227  
228           118. (New) The particle reagent of claim 89, wherein said particles  
229 comprise gold and have an average diameter between 80 and 120 nanometers  
230 inclusive.

231  
232           119. (New) The particle reagent of claim 89, wherein said particles  
233 comprise gold and have an average diameter greater than 120 nanometers and less  
234 than one micrometer.

236 120. (New) The particle reagent of claim 89, wherein said particles  
237 comprise silver and have an average diameter between 5 and 50 nanometers.  
238

239 121. (New) The particle reagent of claim 89, wherein said particles  
240 comprise silver and have an average diameter between 20 and 100 nanometers.  
241

242 122. (New) The particle reagent of claim 89, wherein said particles  
243 comprise silver and have an average diameter between 10 and 200 nanometers.  
244

245 123. (New) The particle reagent of claim 89, wherein said particles  
246 comprise silver and have an average diameter of 120 nanometers or less.  
247

248 124. (New) The particle reagent of claim 89, wherein said particles  
249 comprise silver and have a diameter selected from the group consisting of 10, 20,  
250 30, 40, 60, and 100 nm.  
251

252  
253 125. (New) A multiparticle optical signal agent comprising  
254 at least one particle formed of a magnetic or ferro electrical material,  
255 attached to  
256 at least one metal-like particle.  
257

258 126. (New) The multiparticle optical signal agent of claim 125, wherein at  
259 least one said metal-like particle comprises silver or gold.  
260  
261

262 127. (New) A method for making specifically detectable coated gold  
263 particles, comprising:  
264 contacting a population of seed particle having a size between about 1 and  
265 20 nanometers in diameter with a gold chloride solution and a hydroxylamine

hydrochloride solution under conditions in which the size of the resulting gold particles has a coefficient of variation of less than 10%; and  
attaching a specific binding agent or a molecule for binding of a binding agent to said particles.

128. (New) The method of claim 127, wherein the size of said resulting gold particles has a coefficient of variation of less than 5%.

129. (New) The method of claim 127, wherein said resulting gold particles have a diameter of between 10 and 45 nanometers inclusive.

130. (New) The method of claim 127, wherein said resulting gold particles have a diameter of between 50 and 70 nanometers inclusive.

131. (New) The method of claim 127, wherein said resulting gold particles have a diameter of between 80 and 120 nanometers inclusive.

132. (New) The method of claim 127, wherein said resulting gold particles have a diameter of greater than 120 nanometers and less than one micrometer.

133. (New) The method of claim 127, wherein said seed particles are gold.

134. (New) The method of claim 127, wherein said seed particles are silver.

135. (New) A method for making specifically detectable coated silver particles, comprising:

contacting a population of seed particle with a silver salt solution under conditions such that silver is deposited on said seed particles; and

295           attaching a specific binding agent or a molecule for binding of a binding agent  
296   to said particles.

297  
298           136. (New) The method of claim 135, wherein said seed particles are gold.

299  
300           137. (New) The method of claim 135, wherein said seed particles are silver.

301  
302           138. (New) The method of claim 135, wherein the resulting particles have  
303   an average diameter of 20-100 nm.

304  
305           139. (New) The method of claim 135, wherein the resulting particles have  
306   an average diameter of 10-200 nm.

307  
308           140. (New) The method of claim 135, wherein the size of the resulting  
309   particles has a coefficient of variation of less than 15%.

310  
311           141. (New) The method of claim 135, wherein the size of the resulting  
312   particles has a coefficient of variation of less than 10%.

313  
314           142. (New) The method of claim 135, wherein the size of the resulting  
315   particles has a coefficient of variation of less than 5%.

316  
317  
318           143. (New) A test kit, comprising  
319           a plurality of at least one type of metal-like light scattering particles,  
320   wherein the particles are between 1 and 500 nm in diameter, and wherein different  
321   particle types, when present, are adapted to bind to different analytes; and  
322           a solid phase array comprising a plurality of binding agents bound at a  
323   plurality of spatially addressable spots.

325           144. (New) The kit of claim 143, wherein said plurality of binding agents  
326 bind to a plurality of different analytes.

328           145. (New) The kit of claim 144, wherein said plurality of binding agents  
329 comprises a plurality of nucleic acid molecules.

331           146. (New) The kit of claim 144, wherein said plurality of binding agents  
332 comprises a plurality of antibodies.

334           147. (New) The kit of claim 144, wherein said plurality of binding agents  
335 comprises a plurality of receptors.

337           148. (New) The kit of claim 144, wherein said plurality of binding agents  
338 comprises a plurality of proteins.

340           149. (New) The kit of claim 144, wherein said plurality of binding agents  
341 comprises a plurality of peptides.

343           150. (New) The kit of claim 144, wherein said plurality of binding agents  
344 comprises a plurality of pharmaceutical agents.

346           151. (New) The test kit of claim 143, wherein said at least one metal-like  
347 light scattering particle type comprises a plurality of distinguishable particle types.

349           152. (New) The test kit of claim 143, wherein said at least one metal-like  
350 light scattering particle type comprises a plurality of distinguishable metal light  
351 scattering particle types.

353           153. (New) The test kit of claim 152, wherein each of said plurality of  
354 different particle types provides a different color of scattered light on illumination  
355 with white light.

356  
357           154. (New) The test kit of claim 143, wherein the particles of a particle  
358 type have on their surfaces a binding agent that binds to an analyte.

359  
360           155. (New) The test kit of claim 143, wherein the particles of a particle  
361 type are adapted to indirectly bind to an analyte.

362  
363           156. (New) The test kit of claim 143, wherein the particles of a particle  
364 type comprise gold.

365  
366           157. (New) The test kit of claim 143, wherein the particles of a particle  
367 type comprise silver.

368  
369           158. (New) The test kit of claim 143, wherein the particles of a particle  
370 type comprise gold and silver.

371  
372           159. (New) A test kit, comprising  
373 a plurality of populations of different distinguishable metal-like light scattering  
374 particle types, wherein the particles are between 1 and 500 nm and different  
375 particle types are adapted to bind to different analytes.

376  
377  
378           160. (New) The test kit of claim 159, wherein the particles of a particle  
379 type comprise a binding agent that binds to an analyte.

380  
381           161. (New) The test kit of claim 159, wherein the particles of a particle  
382 type are adapted to indirectly bind to an analyte.

383

384           162. (New) The test kit of claim 159, wherein the particles of a particle  
385 type comprise gold.

386

387           163. (New) The test kit of claim 159, wherein the particles of a particle  
388 type comprise silver.

389

390           164. (New) The test kit of claim 159, wherein the particles of a particle  
391 type comprise gold and silver.

392

393           165. (New) The test kit of claim 159, wherein each of said plurality of  
394 populations of different particle types provides a different color of scattered light on  
395 illumination with white light.

396

**REMARKS**

Support for the preceding new claims is provided in the original claims, in the claims of the related provisional application, and in the specification. Thus, no new matter is presented.

Applicant believes that the present application is now in condition for allowance. Favorable consideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date

16 August 2001

By

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